Recurrent thromboembolism in patients with vena cava filters

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Background: **Patients with venous thromboembolic disease are treated with anticoagulation or vena cava filter placement to prevent pulmonary embolism. A recent report suggested that filter placement may increase the risk of recurrent deep venous thrombosis (DVT) and prompted a review of our experience.**
Methods: **Prospectively collected data on 2109 consecutive patients receiving filters were evaluated for recurrent thromboembolism, vena cava occlusion, or venous stasis ulceration. Outcomes were stratified and analyzed according to the use of anticoagulants at the time of insertion and at follow-up. Incidence rates were also compared with reports in the literature.**
Results: **Of 1191 patients with DVT at filter placement, complete follow-up data at a mean of 9 years were available for 465. Recurrent DVT was found in 12% of the 241 patients who were given anticoagulants and 15% of the 224 who were not ($P > .05$). We also failed to find a significant association between the use of anticoagulation and the incidence of pulmonary embolism (2%), stasis ulceration (2%), and vena cava occlusion (0.0).**
Conclusions: **Recurrent DVT in patients with existing thromboembolic disease is not an unexpected event, which, in our experience, is not associated with anticoagulant or filter use. Anticoagulation should be used when possible to treat existing DVT to reduce thrombus progression and potentially to reduce subsequent complications but does not seem to reduce the rate of recurrent DVT. Rates of recurrent thromboembolism were consistently less than the 20% to 50% reported in the literature. (J Vasc Surg 2001;33:510-4.)**

Vena cava filtration is standard treatment for patients with thromboembolic disease who are unable to receive anticoagulants or are at such risk from pulmonary embolism that additional protection is required. Because the filter has no effect on the underlying venous disease, anticoagulants are recommended in conjunction with the filter whenever possible to prevent recurrent thromboembolism and postthrombotic sequelae. The outcomes for patients who cannot receive anticoagulants remains uncertain, although a recent study of filter use in connection with heparin suggested that filter placement could increase the risk of recurrent deep venous thrombosis (DVT).[1] Early in our experience we studied the importance of anticoagulation and were unable to find a difference in the outcomes of more than 100 cases.[2] This review extends that experience to more than 1024 patients who had filters placed in the presence of acute thrombosis and were monitored for 3053 person-years.

METHODS

The Michigan Filter Registry has been maintained continuously since 1972 and contains prospectively collected data for 2109 consecutive patients treated by the senior author over a 28-year period. The entry record contains information on medical status, presence and extent of objectively diagnosed thromboembolic disease, treatments, and details of filter placement.

Patients receive an annual reminder letter to schedule a follow-up appointment, which includes physical examination, abdominal radiography, and lower extremity vein and inferior vena cava duplex ultrasound examinations. The follow-up record includes physical examination of the extremities, medical history since filter placement, recurrence of pulmonary embolism (PE), and objective tests for filter patency, DVT, chronic venous insufficiency, and stability of the filter. The rate of follow-up for the entire registry is 54%, and the mean length of follow-up exceeds 5 years. These data are maintained in a 4th Dimension database, Version 6.0 for the Macintosh (4D Inc, San Jose, Calif).

Patients with acute DVT or PE at the time of filter placement comprise the study cohort. Information on anticoagulation was limited to the type of agent and the time it was used relative to filter placement. These cases were stratified according to the use of anticoagulants either during the postprocedural period or during subsequent follow-up and analyzed on the basis of subsequent complications. Four outcomes were evaluated; new DVT, PE, caval occlusion, or venous ulceration. New DVT was diagnosed on the basis of color-flow Doppler-duplex studies. Both extremities were scanned from above the groin to the ankle. Lack of compressibility or visualization of thrombus were the criteria for a positive diagnosis. Thrombus was characterized as acute or chronic and whether it was a new abnormality or a previous finding. Information regarding new PE was based on patient reports or diagnostic studies performed during the prior interval. All reports of PE, whether reported by the

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Table I. Demographic data for filter patients with thromboembolic disease

	Anticoagulation (n = 487)	*No anticoagulation (n = 637)*
Age (y)	54 (12-93)	58 (19-93)*
Male	253 (52%)	333 (48%)
Mortality	167 (34%)	302 (48%)
Survival	59 mo	47 mo*
Follow-up		
All cases	241 (50%)	224 (35%)
Survived 1 year	206 (64%)	178 (52%)

*$P < .05$.

Table II. Filter placement details by percent in each category

	Anticoagulant (n = 487)	*No anticoagulant (n = 637)*
Number of filters		
1	100%	99.9%
2	0	.1%
Inserted		
Radiology	80%	74%
Surgery	20%	26%
Method		
Percutaneous	80%	72%
Surgical	20%	28%
Type of filter		
PSGF	32%	20%
SGF	22%	33%
TGF	44%	45%
Other	2%	2%
Filter location		
Infrarenal	92.1%	91.7%
Suprarenal	7.5%	7.6%
Superior vena cava	0.3%	0.2%
Misplaced	1%	0.5%
Route		
Missing	3%	2%
Jugular	28%	11%
Femoral	67%	81%
Other	2%	1%
Insertion problems		
Asymmetry	2.6%	1.7%
Tilt	0.2%	1%
Crossed legs	0.2%	0.2%
Incomplete opening	0.8%	0.2%
Placement morbidity		
Leg swelling	0	0.8%
Hematoma	2%	1%
Infection	0	0.3%
Bleeding	0.8%	0.5%

PSGF, Percutaneous stainless steel Greenfield filter; *SGF,* stainless steel Greenfield filter; *TGF,* titanium Greenfield filter.

patient or documented by objective testing, were treated as confirmed. Filter or caval occlusion was diagnosed by Doppler-duplex ultrasound scanning. The cava was considered occluded if the filter could not be visualized and Doppler signals were absent.

Reports of occlusion on the basis of vena cavograms or computed tomography scans were also included in this category. Venous ulceration was documented with observation at the time of the lower extremity study. Findings of edema and use of support stockings were based on observation during the lower extremity study and patient reports.

Statistical analyses were conducted with Systat version 5.0 for the Macintosh (Systat, Evanston, Ill) and SAS V.6.12 (SAS Institute, Cary, NC). Continuous data were compared with the Student *t* test, whereas the Fisher exact test or likelihood ratio χ^2 tests were used with dichotomous outcomes. We evaluated the null hypothesis of no association between the use of anticoagulants after filter placement and the incidence of new thromboembolic events or vena cava occlusion. Because four comparisons were involved in the primary analysis, the *P* value was adjusted with a Bonferroni correction, with *P* less than .0125 being considered significant. Additional exploratory analyses were conducted to generate new research questions regarding the association between underlying disease, indication for filter placement, and the use of anticoagulation. The *P* value was not corrected for these comparisons. Survival analyses with life-table methods and Kaplan-Meier plots were generated, and group comparisons were made with the log-rank test.

RESULTS

A cohort of 1191 patients with acute DVT at the time of filter placement was identified. It represented 54% of the database. Sixty-seven of the 1191 patients were given anticoagulants at some time during the initial hospitalization, but the timing relative to filter placement was unknown, leaving 1124 cases included in the analyses. Table I summarizes the demographic information showing that the groups were comparable with respect to age and sex but showed a clinically important difference in mortality rates and length of survival that favored those who were given anticoagulants. Table II describes the related procedural events that are similar for the two groups. Tables III and IV report the indications for filter placement and primary diagnoses for each group.

Data were complete for 465 patients who had at least one follow-up appointment. The patient groups differed in that those without follow-up had a higher incidence of cancer as the primary diagnosis. This probably explains the higher mortality rate, shorter survival time, and higher rate of PE-related death (Table V). The incidence of new DVT in this cohort was 13.3%. PE was suspected or confirmed in 3%, and caval occlusion occurred in 0.4%. Mean survival was 57.7 months, 95% CI (53.8, 61.3). Survival is depicted in Fig 1.

Among those who had follow-up, 241 were given anticoagulants and 224 were not. We failed to reject the null hypothesis for the major outcomes of interest; for new PE, DVT, cava occlusion, or venous ulceration, however, the survival rate was different (Fig 1, Table V). Specifically, among those patients who were examined for follow-up, the difference in the incidence of new DVT (3%, $P = .35$) and PE (2%, $P = .16$) failed to reach statistical significance,

Table III. Primary underlying diagnosis related to use of anticoagulation

	Anticoagulation (n = 487)	*No anticoagulation (n = 637)*
Thromboembolism	32%	20%*
Malignancy	20%	27%*
Trauma	10%	8%
Cardiac	4%	5%
Pulmonary	2%	2%
Surgery	24%	26%
Other	8%	12%

*P value < .05.

Table IV. Indications for filter placement related to use of anticoagulation

	Anticoagulation (n = 487)	*No anticoagulation (n = 637)*
Anticoagulant contraindication	23%	62%
Anticoagulant complication	17%	18%
Recurrent PE	15%	3%
Prophylaxis	40%	14%
Embolectomy	1%	0.4%
Missing	4%	2.6%

Table V. Comparison of patients stratified by use of anticoagulants and follow-up

	Anticoagulation		*No anticoagulation*	
	Follow-up	*No follow-up*	*Follow-up*	*No follow-up*
No.	263	292	225	418
Male sex	54%	53%	48%	54%
Mean age in years	53.2	55.9	55.4	57.4
Diagnosis of cancer	10.4%	28.5%	13.8%	33.3%
Mean survival in mo	75.6	32.7	75.3	38.4
Mortality	14%	56%	20%	61%
PE-related morbidity	0	1%	0	1%

and the incidence of inferior vena cava occlusion was identical for the two groups at less than 1%. Fig 2 depicts the lack of association between new DVT and anticoagulant use (P = .36 log-rank test). Lower extremity edema was similar in the two groups, but twice as many patients wore support stockings to control symptoms of venous insufficiency in the no-anticoagulation group (P = .006). This suggests that anticoagulation may modify the long-term sequelae of DVT. In subsequent follow-up visits, anticoagulation was used more often in those who had been given anticoagulants initially after filter placement, and this group experienced twice the number of anticoagulant complications while receiving long-term anticoagulation than those who had not been given anticoagulants initially (Table VI). Patients with a history of thromboembolism were given anticoagulants more frequently than those without (P < .0001, Table III).

As expected, contraindication to anticoagulation accounted for a greater percentage of cases in the no-anticoagulation group (P < .0001, Table IV). No distinction between relative and absolute contraindication was made. With careful evaluation and follow-up, it is possible to safely give anticoagulants to most patients once the contraindication has resolved. This may especially be true where the contraindications were relative or weak. Sixty-one patients were given anticoagulants after filter placement in the group who had received anticoagulation, and 81 of the patients in the no-anticoagulation group were given anticoagulants during 1 or more years after filter placement.

DISCUSSION

This study is based on data from a registry that has inherent limitations; detailed patient information regarding level and length of anticoagulation is not available, the groups are not randomized and the rate of follow-up is low (52%-64%). Methods of testing for recurrent DVT changed over time from duplex ultrasound scanning to color flow Doppler scanning. We do not track prothrombin time, international normalized ratio, or activated partial thromboplastin time values, so it is not possible to comment on the patients' level of anticoagulation, only whether it was ordered. This limits the strength of our findings. However, these data were collected prospectively from consecutive cases, and the numbers are large. These factors must be considered when weighing the validity of our conclusions. With respect to recurrent DVT and PE, cava occlusion and stasis ulceration, the differences between the groups failed to reach statistical significance; however, a post hoc analysis found the power of the study to detect a difference was low. More important, however, the differences were clinically insignificant. In this patient cohort, the clinical difference is probably the more useful, allowing physicians to determine the importance to their own practice. Our findings suggest that it is the underlying thrombotic risk that is associated with recurrent thromboembolic events and sequelae rather than the presence of the filter.

In a previous animal study, Greenfield filters were placed in mongrel dogs and filled with autologous throm-

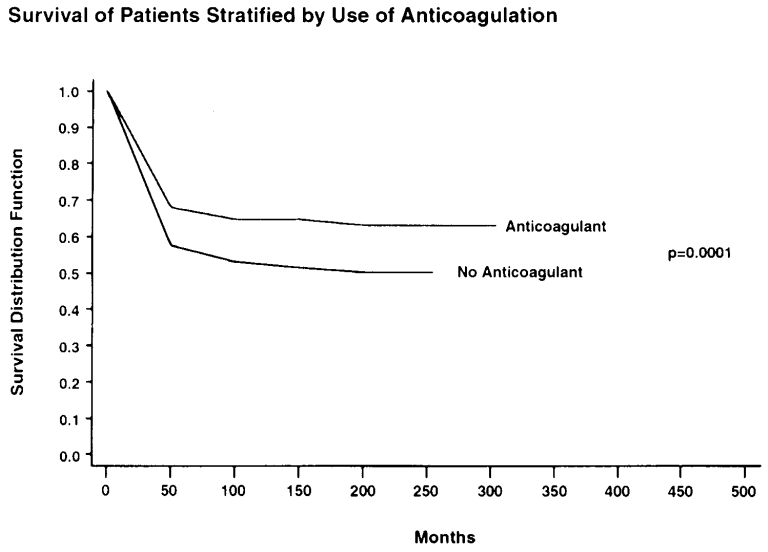

Fig 1. There was a difference in mortality rate that was associated with use of anticoagulation.

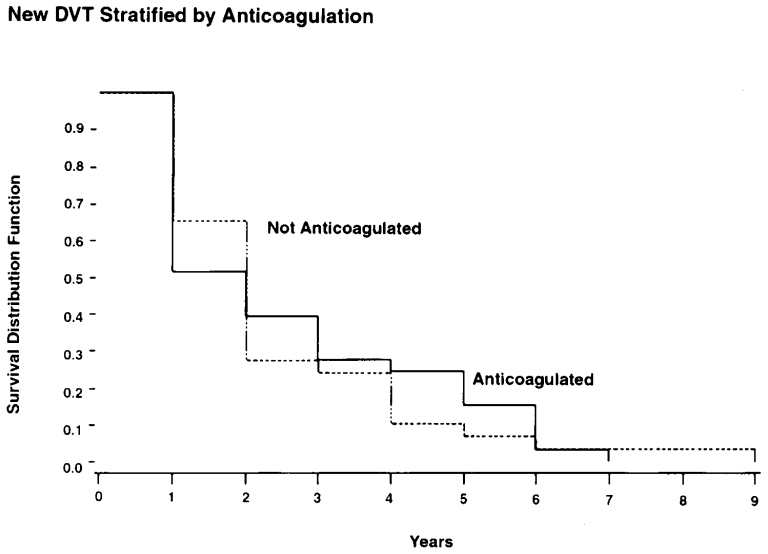

Fig 2. There was no difference in timing of new DVT that was associated with use of anticoagulation.

bus. The animals were randomly assigned to receive heparin, warfarin (Coumadin), or no anticoagulants. Logistic regression analyses demonstrated that thrombus resolution was associated with the initial thrombus burden and elapsed time from filter placement, not the use of anticoagulants.[3] These differences were found in spite of the presence of the filter in all animals.

Meissner et al[4] reached the same conclusion in a clinical study where the only risk factor significantly associated with recurrent DVT was the extent of thrombus burden at the initial thromboembolic event. Regression analysis showed that in a model including age, diagnosis, and anticoagulation, the only factor associated with the new DVT was the underlying diagnosis ($P < .02$). In an earlier analysis of our data on anticoagulation in patients with filters, nine new thromboembolic events occurred, and six were among those who were given anticoagulants, suggesting that there was some inherent difference among the groups that resulted in recurrent thromboembolism other than the use of anticoagulants.[2]

The literature regarding vena cava filters and the use of anticoagulation is conflicted. It supports the utility of anticoagulation for treating underlying venous disease among patients with filters, but it also indicates that anticoagulation is not associated with statistically significant differences in recurrence of thromboembolic events or sequelae

Table VI. Long-term results in patients who had follow-up stratified with anticoagulation at time of filter insertion

	Anticoagulation (n = 241)	*No anticoagulation (n = 224)*
New DVT	12%	15%
Recurrent PE	4%	2%
IVC occlusion	0.4%	0.4%
Ulceration	4%	6%
Edema	56%	55%
Stockings	17%	34%*
Anticoagulation during follow-up	61%	36%*
Anticoagulant complication	7%	3.6%

*P value < .05.
IVC, Inferior vena cava.

of venous thromboembolism. Both Cugell[5] and Harris et al[6] support the use of anticoagulation on the basis of the assumption that it should lower the risk of recurrent embolism or phlegmasia cerulea dolens in patients with filter placement, reinforcing the importance of continuing to treat the underlying venous disease when possible. However, Ortega et al[7] and Jones et al[8] failed to observe this proposed benefit.

The incidence of recurrent thromboembolism in this analysis is similar to estimates we reported in the past, suggesting that the incidence does not change over time.[2,9] However, for individual patients it declined and stabilized after 24 months (Fig 2). DVT recurred in 12% or 15% of patients, depending on whether anticoagulation was used, which is similar to other series.[10] Meissner et al[4] studied 177 patients with DVT during a 7-year period and a median follow-up of 9 months and found that recurrent thrombotic events (either rethrombosis, extension, or new DVT) occurred in 52% of patients. This was true in spite of the fact that between 59% and 88% of patients were given anticoagulants and were not given filters.

Mortality rates differed among the groups, favoring those who received anticoagulation, which may be due to an important difference in the underlying diagnosis, with the no-anticoagulation group having statistically significantly more patients with cancer than those who were given anticoagulants (Table V). The difference in survival rates remained significantly different when we controlled for both cancer and anticoagulant use. Patients without malignancy continued to demonstrate longer survival relative to patients with cancer. Anticoagulation appears to be associated with improved survival rates among the noncancer group but not among those with cancer. In a full logistic regression model younger age ($P = .005$), anticoagulation ($P = .0375$) and the status of the thromboembolic event ($P = .001$) were associated with superior survival rates. This finding requires further investigation.

A group of French investigators studied the interaction of filters and anticoagulants from an alternative perspective examining the effect of filter placement in addition to anticoagulation in patients diagnosed with DVT or PE.[1] These patients represent a very different population than our own. The authors reported that in spite of failing to enroll sufficient numbers of patients, they were still able to demonstrate a statistically significant benefit of the filter with respect to preventing new PE within the first 12 days. However, when they looked at the incidence of DVT 2 years later, they found that the rate was significantly higher in the patients with filters and concluded that the initial benefit of the filter was offset by this increased incidence of DVT at 2 years. Unfortunately, there was not sufficient information to evaluate their findings, especially with respect to continued use of anticoagulation, underlying disease, patency of the vena cava, and the type of filter that was used.

The decision to use anticoagulation in addition to a vena cava filter and the duration of this therapy should be based on an individual risk/benefit assessment, not from concern for filter-induced thrombosis. After all, the trade-off between a fatal PE and a recurrent DVT is not difficult to assess. Physicians should not hesitate to follow their customary patterns for use of vena cava filters or feel a need to prolong anticoagulant use out of concern for a potential increased recurrence of DVT because there is no evidence to support that assumption.

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Please see related commentary by Dr John J. Ricotta on page 657.